PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	06.07.2004
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
E 7794/WM/	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/03541	04.04.2003	05.04.2002

Applicant
EURO-CELTIQUE S.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
E 7794/WM/		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/03541	04.04.2003	05.04.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K9/16		
Applicant		
EURO-CELTIQUE S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.08.2003	06.07.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03541

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-58 as originally filed

Claims, Numbers

1-40 received on 14.06.2004 with letter of 14.06.2004

Drawings, Sheets

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11-15,25-40
	No:	Claims	1-10,16-24
Inventive step (IS)	Yes:	Claims	11-15,25,26,33-40
	No:	Claims	1-10,16-24,27-32
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: EP-A-0 699 436 (EURO CELTIQUE SA) 6 March 1996 (1996-03-06)
D2: EP-A-0 631 781 (EURO CELTIQUE SA) 4 January 1995 (1995-01-04)

The present invention discloses storage stable pharmaceutical dosage forms and methods of preparations thereof. Particularly, the invention relates to storage stable pharmaceutical dosage forms which comprise at least two pharmaceutically active agent in a (non-swellable) diffusion matrix wherein the matrix is determined with respect to its essential release characteristics by ethylcellulose or an ethylcellulose-based polymer and at least one fatty alcohol and wherein the active compounds are released from the matrix in a sustained, invariant and, where several compounds are present, independent manner.

1. Novelty

Document **D2** (citations see ISR) discloses pharmaceutical dosage forms which comprises opioids and combinations of at least two opioids (e.g. one mu-agonist and one mu-antagonist (see page 3, line 20-line 23)) in a matrix, said matrix comprises Surelease®, a commercial product containing for example ethylcellulose and dibutyl sebacate (as also used in the present application). Another suitable controlled-release matrix comprise an alkylcellulose (especially ethyl cellulose), a aliphatic alcohol, such as lauryl- or myristyl alcohol and, optionally a polyalkylene glycol, such as PEG. In addition to the above mentioned ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, fillers, binders, glidants (e.g. dibutyl sebacate) etc. Naloxone, used in the present application is nowhere mentioned in **D2.** Therefore, present claims 1-10 and 16-24 seem to be not novel over the prior art **D2.**
On the other hand, the subject-matter of claims 11-15 and 25-40 seems to be novel.

2. Inventive step

A person skilled in the art with the problem to develop a sustained release matrix dosage form of a combination of two opioids would start with document D2 since it is dealing with sustained release dosage forms of opoids and even with oxycodone in combination with a mu-antagonist. The methods for producing said storage stable pharmaceutical compositions, as claimed in claims 27-32 are

common knowledge [redacted] a person skilled in the art and wo[redacted]be part of a regular development procedure. Therefore, the subject matter of present claims 1-10, 16-24 and 27-32 seems to not involve an inventive step.

2. **Industrial applicability**

Present claims 1-40 are all industrial applicable.

PCT/EP03/03541
EURO-CELTIQUE S.A.

14 June 2004

New Claims

1. Storage stable pharmaceutical formulation comprising at least two pharmaceutically active compounds in a diffusion matrix,

characterized in that the matrix is determined with respect to its essential release characteristics by ethylcellulose or an ethylcellulose-based polymer and at least one fatty alcohol and that the active compounds are released from the substantially non-swellable diffusion matrix in a sustained, invariant and independent manner.

2. Pharmaceutical formulation according to claim 1,

characterized in that the fatty alcohol comprises lauryl, myristyl, stearyl, cetylstearyl, ceryl and/or cetylalcohol, preferably stearyl alcohol.

3. Pharmaceutical formulation according to claim 1 or 2,

characterized in that the formulation comprises ethylcellulose.

4. Pharmaceutical formulation according to one of the preceding claims,

characterized in that the formulation does not comprise relevant amounts of alkaline and/or water-swellable substances, particularly derivatives of acrylic acid and/or hydroxyalkylcelluloses.

5. Pharmaceutical formulation according to one of the preceding claims,

characterized in that the formulation comprises common pharmaceutical excipients, particularly fillers, lubricants, flowing agents and/or plasticizers.

6. Pharmaceutical formulation according to claim 5,

characterized in that the fillers are selected from the group comprising sugars, preferably lactose, glucose and/or saccharose, starches and hydrolysates thereof, preferably micro-crystalline cellulose and/or cellactose, sugar alcohols, preferably sorbitol and/or

WM:HG:bm

mannitol, poorly soluble calcium salts, preferably calcium hydrogenphosphate, dicalciumphosphate or tricalciumphosphate and/or povidone.

7. Pharmaceutical formulation according to claim 5,
characterized in that it comprises magnesium stearate, calcium stearate and/or calcium laureate and/or fatty acids, preferably stearic acid as lubricant.

8. Pharmaceutical formulation according to claim 5,
characterized in that it comprises highly dispersed silica, preferably Aerosil®, talcum, corn starch, magnesium oxide, magnesium and/or calciumstearate as flowing agent.

9. Pharmaceutical formulation according to claim 5,
characterized in that it comprises dibutyl sebacate as plasticizer.

10. Pharmaceutical preparation according to one of the preceding claims,
characterized in that the formulation can be stored over a period of at least two years under standard conditions (60% relative humidity, 25°C) in accordance with admission guidelines.

11. Pharmaceutical preparation according to one of the preceding claims,
characterized in that it comprises as the pharmaceutically active compounds at least one opioid analgesic selected from the group comprising morphine, oxycodone, hydromorphone, propoxyphene, nicomorphine, dihydrocodeine, diamorphine, papaveretum, codeine, ethylmorphine, phenylpiperidine and derivatives thereof, methadone, dextropropoxyphene, buprenorphine, pentazocin, tilidine, tramadol and hydrocodone and at least one opioid antagonist, selected from the group comprising naltrexone, naloxone, nalmefene, nalorphine, nalbuphin, naloxonazinene, methylnaltrexone, ketylcyclazocine, norbinaltorphimine, naltrindol, 6-β-naloxol and 6- β-naltrexol.

12. Pharmaceutical formulation according to claim 11,
characterized in that the opioid analgesic and the antagonist are present in the form of their pharmaceutically acceptable and equally active derivatives, such as the free base, salts

and the like, preferably as the hydrochloride, sulfate, bisulfate, tatrate, nitrate, citrate, bitatrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.

13. Pharmaceutical formulation according to claim 11 or 12,

characterized in that the formulation comprises oxycodone and naloxone, and wherein oxycodone is present in an amount ranging from 10 to 150 mg, preferably from 10 to 80 mg and naloxone is present in an amount ranging from 1 to 50 mg per unit dosage.

14. Pharmaceutical formulation according to claim 13,

characterized in that it comprises oxycodone and naloxone in a weight ratio ranging from maximal 25:1, preferably maximal 20:1, 15:1 and more preferably from 5:1, 4:1, 3:1, 2:1 and 1:1.

15. Pharmaceutical formulation according to claim 11 or 12,

characterized in that it contains oxycodone and naloxone with oxycodone being present in an amount ranging from 10 to 150 mg, preferably from 10 to 80 mg and naloxone being present in an amount ranging from 1 to 50 mg.

16. Pharmaceutical preparation according to one of the preceding claims,

characterized in that the formulation is a tablet, preferably a multi-layered tablet, a capsule, a dragée, a granulate and/or a powder.

17. Pharmaceutical formulation according to claim 16,

characterized in that the pharmaceutical preparation is suitable or oral, nasal and/or rectal application.

18. Pharmaceutical formulation according to one of the preceding claims,

characterized in that the formulation is produced by build-up and/or break-down granulation, preferably by spray granulation.

19. Pharmaceutical formulation according to one of claims 1 to 17,

characterized in that the formulation is produced by extrusion.

20. Storage stable pharmaceutical formulation comprising at least two active compounds in a sustained release matrix,

characterized in that the matrix is a substantially non-swellable diffusion matrix whose release characteristics are determined by amounts of ethylcellulose or an ethylcellulose-based polymer and at least one fatty alcohol as matrix components, and by extrusion or granulation of the matrix materials together with the amount of the active compounds for formation of an active compound-containing matrix.

21. Storage stable pharmaceutical formulation according to claim 20, wherein the diffusion matrix is a substantially non-erosive matrix.

22. Storage stable pharmaceutical formulation according to claim 20 or 21, wherein the matrix material contains ethylcellulose.

23. Storage stable pharmaceutical formulation according to one of claims 20 to 22, wherein the matrix is formed by extrusion, particularly by melt extrusion.

24. Storage stable pharmaceutical formulation having an effective amount of an opioid agonist and an opioid antagonist in a substantially non-swellable and non-erosive diffusion matrix, whose release characteristics are determined by amounts of ethylcellulose or an ethylcellulose-based polymer and at least one fatty alcohol.

25. Storage stable pharmaceutical formulation according to claim 24 having an effective amount of oxycodone and naloxone, with oxycodone being present in an amount ranging from 10 to 150 mg, preferably from 10 to 80 mg and naloxone being present in an amount ranging from 1 to 50 mg per unit dosage.

26. Storage stable pharmaceutical formulation according to claim 24 or 25 having an effective amount of oxycodone and naloxone, wherein oxycodone and naloxone are present in a weight ratio ranging from maximal 25:1, preferably maximal 20:1, 15:1, particularly preferably 5:1, 4:1, 3:1, 2:1 and 1:1.

27. Method for producing a formulation according to one of claims 1 to 26, **characterized in that** granulation, preferably build-up and/or break-down granulation, particularly preferably spray granulation is used.

28. Method of producing a formulation according to one of claims 1 to 26, being an extrusion method, wherein counter-rotating or co-rotating single or multiple screw extruders with/without kneading elements are used.

29. Method according to claim 28, being an extrusion method wherein counter-rotating twin-screw extruders, preferably without kneading elements, are used.

30. Method according to claim 28 or 29, **characterized in that** the temperature of the heating zones of the extruders is between 20°-120°C, preferably between 50°-100°C, more preferably between 50°-90°C and even more preferably between 50°-70°C.

31. Method according to one of claims 28 to 30, **characterized in that** the diameter of the nozzle on the extruder is between 1 to 10 mm, preferably between 2 to 8 mm and particularly preferably between 3 to 5 mm.

32. Method according to one of claims 28 to 31, **characterized in that** the resulting temperature in the extruder does not influence the stability of the active compounds.

33. Method of producing a pharmaceutical dosage form for the treatment of opioid-induced side effects, **characterized in that** the pharmaceutical dosage form comprises a pharmaceutical formulation according to one of claims 1 to 10.

34. Method according to claim 33,

characterized in that the preparation is used for treatment of opioid-induced obstipation and preferably for treatment of opioid-induced pruritus.

35. Method of producing a pharmaceutical dosage form for the treatment of idiopathic syndromes,

characterized in that the pharmaceutical dosage form comprises a pharmaceutical formulation according to one of claims 1 to 10.

36. Method according to claim 35,

characterized in that the preparation is used for treatment irritable bowel syndrome, preferably for treatment of idiopathic pruritus or pruritus due to cholestasia and/or renal dysfunction.

37. Method according to one of claims 33 to 36,

characterized in that the matrix is a substantially non-swellable diffusion matrix whose release characteristics are determined by amounts of ethylcellulose or an ethylcellulose-based polymer and of at least one fatty alcohol.

38. Method according to one of claims 33 to 37,

characterized in that the preparation comprises between approximately 1 to 50 mg naloxone, preferably between approximately 5 to 30 mg naloxone and even more preferably between approximately 5 to 20 mg naloxone.

39. Method according to one of claims 33 to 38,

characterized in that naloxone is present in the form of its pharmaceutically acceptable and equally active derivatives, such as the free base, salts and the like, preferably as the hydrochloride, sulfate, bisulfate, tatrate, nitrate, citrate, bitatrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.

40. Method according to one of claims 33 to 39,

characterized in that the matrix is produced by extrusion.